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# DIFFERENTIATED ANTIPLATELET AND HEPATOPROTECTIVE THERAPY IN PATIENTS WITH STABLE CORONARY HEART DISEASE ON THE BACKGROUND OF NONALCOHOLIC FATTY LIVER DISEASE IN STAGE OF STEATOSIS

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# ДИФЕРЕНЦІЙОВАНА АНТИТРОМБОЦИТАРНА ТА ГЕПАТОПРОТЕКТОРНА ТЕРАПІЯ У ХВОРИХ НА СТАБІЛЬНУ ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ НА ТЛІ НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ В СТАДІЇ СТЕАТОЗУ

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# ДИФФЕРЕНЦИРОВАННАЯ АНТИТРОМБОЦИТАРНАЯ И ГЕПАТОПРОТЕКТОРНАЯ ТЕРАПИЯ У БОЛЬНЫХ СО СТАБИЛЬНОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА НА ФОНЕ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ В СТАДИИ СТЕАТОЗА

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***Abstract.*** **The objective of the research** was to evaluate the effectiveness of long-term antiplatelet and hepatoprotective differentiation therapy in patients with postinfarction cardiosclerosis and co-existent non-alcoholic fatty liver disease in stage of steatosis.

**Materials and methods.** There were examined 72 patients with stable coronary heart disease functional classes II-III and co-existent non-alcoholic fatty liver disease in stage of steatosis. All the patients underwent a complete clinical examination; the functional state of their liver and platelet haemostasis were assessed. All patients received standard therapy the effectiveness of which was assessed 3 and 6 months after treatment.

**Results.** The effectiveness of antiplatelet therapy was found to depend on treatment duration, the functional state of the liver and the scheme of antiplatelet and hepatoprotective differentiation therapy. In particular, 6 months after treatment, a positive dynamics of platelet haemostasis was observed in all the patients of Group I. However, the target value of its indicators was achieved in 60.5% of patients. In Group II, the target level of platelet aggregation activity was achieved in 38.3% of patients. The level of liver enzymes was within the control limits in 52.8% of patients. In 47.2% of patients, however, an increase in their level was observed, which necessitated the administration of appropriate hepatoprotective therapy.

**Conclusions.** The developed concept of differentiation treatment of patients with coronary heart disease and co-existent non-alcoholic fatty liver disease in stage of steatosis envisages the need for monitoring the indicators of platelet haemostasis and liver function every three months after the administration of antiplatelet therapy with the possibility of its intensification and the inclusion of hepatoprotective drugs.

***Keywords: stable coronary heart disease; non-alcoholic fatty liver disease; antiplatelet therapy***

***Резюме.*** Метою дослідження було оцінити ефективність тривалої диференційованої антитромбоцитарної та гепатопротекторної терапії у хворих із постінфарктним кардіосклерозом на тлі неалкогольної жирової хвороби печінки (НАЖХП) у стадії стеатозу. **Матеріал та методи.** Об'єктом дослідження стали 72 хворих на стабільну ішемічну хворобу серця (ІХС) ФК II-III, поєднану з НАЖХП у стадії стеатозу. Проводили загальноклінічне обстеження, оцінку функціонального стану печінки та тромбоцитарної ланки гемостазу. Хворі отримували стандартну терапію, оцінку ефективності якої проводили через 3 та 6 місяців лікування. **Результати.** Встановлено, що ефективність антитромбоцитарної терапії (АТТ) залежить від тривалості лікування, функціонального стану печінки, обраної схеми диференційованої АТТ та гепатопротекторної терапії. Зокрема, у всіх хворих І групи через 6 місяців лікування спостерігали позитивну динаміку змін тромбоцитарної ланки гемостазу. Однак цільового значення її показників вдалось досягнути в 60,5% хворих. У ІІ групі через 6 місяців терапії цільовий рівень показників агрегаційної активності тромбоцитів був досягнутий у 38,3% хворих. У 52,8% хворих рівень печінкових ферментів знаходився в межах контролю. Натомість, у 47,2% хворих спостерігали наростання їх рівня, що обумовило необхідність призначення відповідної гепатопротекторної терапії. **Висновки.** Розроблена концепція диференційованого лікування хворих на стабільну ІХС, поєднану з НАЖХП у стадії стеатозу, передбачає необхідність контролю показників тромбоцитарного гемостазу та стану печінки кожні три місяці, призначення відповідної АТТ із можливістю її посилення та включення до лікування гепатопротекторних засобів.

***Ключові слова: стабільна ішемічна хвороба серця, неалкогольна жирова хвороба печінки, антитромбоцитарна терапія.***

***Резюме.*** Целью исследования было оценить эффективность длительной дифференцированной антитромбоцитарной и гепатопротекторной терапии у больных с постинфарктным кардиосклерозом на фоне неалкогольной жировой болезни печени (НАЖБП) в стадии стеатоза. **Материал и методы.** Объектом исследования стали 72 больных со стабильной ишемической болезнью сердца (ИБС) ФК II-III и НАЖБП в стадии стеатоза. Проводили общее клиническое обследование, оценку функционального состояния печени и тромбоцитарного звена гемостаза. Больные получали стандартную терапию, оценку эффективности которой проводили через 3 и 6 месяцев лечения. **Результаты.** Установлено, что эффективность антитромбоцитарной терапии (АТТ) зависит от

продолжительности лечения, функционального состояния печени и выбранной схемы дифференцированной АТТ и гепатопротекторной терапии. В частности, у всех больных I группы через 6 месяцев лечения наблюдали положительную динамику изменений тромбоцитарного звена гемостаза. Однако, целевого значения ее показателей удалось достичь в 60,5% больных. У II группе через 6 месяцев терапии целевой уровень показателей агрегационной активности тромбоцитов был достигнут в 38,3% больных. В 52,8% больных уровень печеночных ферментов находился в пределах контроля. В 47,2% больных наблюдали нарастание их уровня, что обусловило необходимость назначения соответствующей гепатопротекторной терапии. **Выводы.** Разработанная концепция дифференцированного лечения больных со стабильной ИБС, совмещенной с НАЖБП в стадии стеатоза предусматривает необходимость контроля показателей тромбоцитарного гемостаза и состояния печени каждые три месяца назначения соответствующей АТТ с возможностью ее усиления и включения в лечение гепатопротекторных средств.

***Ключевые слова: стабильная ишемическая болезнь сердца, неалкогольная жировая болезнь печени, антитромбоцитарная терапія.***

**Problem statement and analysis of the recent research**

Coronary heart disease (CHD) remains one of the greatest challenges facing modern medicine today being the leading cause of death and disability worldwide [2, 5]. The major pathogenetic basis for CHD development is atherosclerosis as well as thrombus formation on the surface affected by atherosclerosis [11]. In addition to cardiovascular diseases, hepatobiliary pathology is also a medical and social problem, since in 60% of cases, liver diseases affect people of working age [8]. The most common chronic hepatobiliary disease is non-alcoholic fatty liver disease (NAFLD), the initial manifestation of which is steatosis [7]. Nowadays NAFLD co-exist with obesity, insulin resistance, dyslipidemia, CHD, type 2 diabetes mellitus and metabolic syndrome as well as plays a key pathogenetic role in their development [10, 14].

However, the mechanisms by which NAFLD increases the cardiovascular risk are not fully understood. It is due to the increase in the formation of atherogenic pro-inflammatory cytokines and procoagulant factors in the liver affected by steatosis [6, 9, 16]. In addition, basic mechanisms leading to NAFLD progression as well as atherogenesis acceleration include dyslipidemia, insulin resistance, high blood pressure, oxidative stress, systemic inflammation, adipokine imbalance, endothelial dysfunction etc. [10]. Furthermore, there are no data to explain why hepatic steatosis does not develop in all the patients at high cardiovascular risk and may not always progress to steatohepatitis and liver cirrhosis. Thus, hepatic steatosis is considered as a risk factor for atherosclerosis even in the absence of metabolic syndrome or other cardiovascular risk factors [14]. Cardiovascular diseases may, in turn, affect the clinical course of NAFLD thereby increasing the possibility of its progression to liver fibrosis and cirrhosis [11, 16].

Therefore, the study of common clinical and pathogenetic mechanisms involved in CHD and NAFLD occurrence with the aim of developing a comprehensive and individual approach to treatment and prevention of such comorbid pathology is intensely relevant to modern medicine [4, 17]. Furthermore, the evaluation of the possibility, effectiveness and safety of using antiplatelet therapy (APT) in stable CHD with co-existent NAFLD is promising.

**The objective of the research** was to evaluate the effectiveness of long-term antiplatelet and hepatoprotective differentiation therapy in patients with postinfarction cardiosclerosis and co-existent NAFLD in stage of steatosis.

**Materials and methods**

There were examined 72 patients (the average age – 53.7±4.6) with stable CHD FC I-II and co-existent NAFLD in stage of steatosis. The control group included 20 apparently healthy individuals.

The diagnosis of stable CHD was verified according to the results of electrocardiography, coronary catherization as well as the presence of myocardial infarction in past medical history in accordance with the unified clinical protocol "Stable Coronary Heart Disease" (Order of the Ministry of Health of Ukraine of 02.03.2016, No 152) [13]. The diagnosis of NAFLD was made according to the unified clinical protocol "Non-Alcoholic Steatohepatitis" (Order of the Ministry of Health of Ukraine of 06.11.2014, No 826) [12], the adapted clinical practice guidelines "Non-Alcoholic Fatty Liver Disease" [1] in accordance with the clinical practice recommendations of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) [15].

All the patients underwent a complete clinical examination (the analysis of complaints, past medical history, life history, physical examination), electrocardiography, echocardiography, coronary catherization, liver ultrasound; the functional state of their liver and platelet haemostasis were assessed.

The functional state of the liver was assessed by serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGTP) using the spectrophotometric method by means of standard kits.

Platelet haemostasis was assessed by the indicators of platelet aggregation activity (the degree of aggregation, the rate of aggregation, platelet aggregation time, platelet count, von Willebrand factor) by means of the aggregometer Solar AP-2110 (Republic of Belarus) using 2.5 jmol/L adenosine diphosphate according to generally accepted standard procedures [3].

All the patients enrolled in our study adhered to the recommendations involving lifestyle modification such as diet therapy and regime of increasing physical activity depending on the time period after acute coronary syndrome and exercise tolerance. According to clinical protocols, they received standard therapy including beta blockers, long-acting nitrates, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors or sartans (if necessary), adjusted doses of statins and acetylsalicylic acid at a dose of 75 mg orally once a day. The effectiveness of therapy was assessed 3 and 6 months after treatment.

Depending on the dynamics of changes in the level of liver enzymes 3 months after treatment, all the patients were

divided into 2 groups: Group I included 38 patients with normal liver enzyme level; Group II included 34 patients with elevated liver enzyme level – 1.5-2 times higher than the normal range.

Six months after treatment, in Group I, APT was effective in 23 cases (subgroup A), while in 15 cases (subgroup B), it was insufficiently effective. In Group II, APT was effective for 13 patients with normal liver enzyme level (subgroup A); APT was found to be insufficiently effective for 13 patients with normal liver enzyme level (subgroup B); in 10 patients with elevated liver enzyme level up to 1.5-2 times as compared to their values observed 3 months after treatment, APT was insufficiently effective (subgroup C). If APT was insufficiently effective, it was corrected 3 and 6 months after treatment and patients with elevated liver enzyme level additionally underwent hepatoprotective differentiation therapy (Fig.1).

The obtained data were statistically processed using spreadsheet software Microsoft Excel and an advanced analytics software package Statistica v. 10.0 StatSoft, USA. A reliable difference between the mean values was assessed using paired Student's t-test. The mean values were presented as (M±m), where M was the mean and m was the standard error of the mean. The results were considered statistically significant at $p<0.05$.

**Results and discussion**

The effectiveness of APT by the indicators of platelet aggregation activity was found to depend on treatment duration, the functional state of the liver and the scheme of antiplatelet and hepatoprotective differentiation therapy (Table 1). In particular, 6 months after treatment, positive dynamics in platelet haemostasis was observed in all the patients of Group I. However, the target value of the indicators of platelet aggregation activity was achieved in 23 (60.5%) patients only. In Group IA, platelet aggregation time increased by 49.4% as compared to the basal level and by 26.8% as compared to that observed 3 months after treatment ($p<0.05$). In Group IB, this indicator increased by 26.6% as compared to its initial value ($p<0.05$); however, it did not reach the level of the control group being only 7.5% higher as compared to the indicator observed 3 months after treatment ($p>0.05$).

Six months after treatment, aggregation rate decreased by 28.8% (Group IA) and 14.8% (Group IB) as compared to the basal level. In Group IA, this indicator reached the level of the control group, while in Group IB, it was 18.4% higher ($p<0.05$). Moreover, the difference between the degree of aggregation 6 months after treatment and the basal level was -9.51 in patients of Group IA and -7.59 in patients of Group IB.

In patients of Group IA, a six-month treatment resulted in the decrease in platelet count by 29.7% as compared to their initial value being 13.1% lower than this indicator 3 months after therapy ($p<0.05$). In patients of Group IB, a six-month treatment resulted in the decrease in platelet count by 23.8% as compared to the initial values ($p<0.05$) being only 5.8% lower than this indicator in the control group ($p>0.05$). At the same time, von Willebrand factor decreased by 27.4% (Group IA) and 18.2% (Group IB) as compared to its initial value ($p<0.05$). The difference between this indicator 6 months after treatment and the basal level was -71.07 in patients of Group IA, while in patients of Group IB, it was -47.23 only.

In Group II, 6 months after treatment, the target level of platelet aggregation activity was achieved in 13 (38.3%) patients only. In Group IIA, platelet aggregation time increased by 47.0% as compared to its initial value and by 25.5% as compared to this indicator observed 3 months after treatment ($p<0.05$). In Group IIB and Group IIC, platelet

**Table 1. Dynamics of platelet haemostasis in patients with stable CHD and co-existent NAFLD in stage of steatosis, (M±m)**

| Indicator, units of measurement | | Control group (n=20) | Patients with stable CHD and co-existent NAFLD in stage of steatosis (n=72) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Basal level | Group I (n=38) | | | Group II (n=34) | | | |
| | | | | 3 months after treatment | 6 months after treatment | | 3 months after treatment | 6 months after treatment | | |
| | | | | | subgroup A (n=23) | subgroup B (n=15) | | subgroup A (n=13) | subgroup B (n=11) | subgroup C (n=10) |
| ADP- induced platelet aggregation | Aggregation time, sec | 15.70 ±1.84 | 10.21 ±0.74* | 12.03 ±0.64* § | 15.25 ±0.73 §¶ | 12.93 ±0.46 *§ | 11.96 ±0.72*§ | 15.01 ±0.38 §¶ | 12.64 ±0.42* § | 12.17 ±0.39* § |
| | Δ | | | | +5.04 | +2.72 | | +4.80 | +2.43 | +1.96 |
| | Aggregation rate, %/sec | 14.13 ±0.30 | 19.64 ±0.40 * | 16.92 ±0.40* § | 13.98 ±0.26 §¶ | 16.73 ±0.26* § | 16.18 ±0.32*§ | 14.27 ±0.26 §¶ | 15.82 ±0.34* § | 15.94 ±0.38* § |
| | Δ | | | | -5.66 | -2.91 | | -5.37 | -3.82 | -3.70 |
| | Aggregation degree, % | 21.08 ±0.68 | 30.23 ±0.56 * | 23.84 ±0.45* § | 20.72 ±0.57 §¶ | 22.64 ±0.73* § | 25.68 ±0.49*§ | 21.36 ±0.48 §¶ | 23.32 ±0.36* § | 23.87 ±0.47* § |
| | Δ | | | | -9.51 | -7.59 | | -8.87 | -6.91 | -6.36 |
| | Platelet count, K/mcL | 268.25 ±10.56 | 377.27 ±14.26* | 305.17 ±11.37 *§ | 265.23 ±10.42 §¶ | 287.34 ±11.26* § | 315.07 ±13.71 * § | 272.19 ±10.48§¶ | 292.46 ±11.34 * § | 305.37 ±11.28 * § |
| | Δ | | | | -112.04 | -89.93 | | -105.08 | -84.81 | -71.9 |
| | Von Willebrand factor, % | 189.26 ±7.19 | 259.49 ±10.57* | 218.57 ±8.46* § | 188.42 ±6.53 §¶ | 212.26 ±8.42* § | 224.63 ±10.80 * § | 192.31 ±6.67§¶ | 208.35 ±8.56* § | 218.35 ±8.49* § |
| | Δ | | | | -71.07 | -47.23 | | -67.18 | -51.14 | -41.14 |

Notes: *– a reliable difference as compared to the control group ($p<0.05$); § – a reliable difference as compared to the basal level ($p<0.05$); ¶ – a reliable difference as compared to the indicator 3 months after treatment ($p<0.05$); Δ – the difference between the indicator observed 6 months after treatment and the basal level

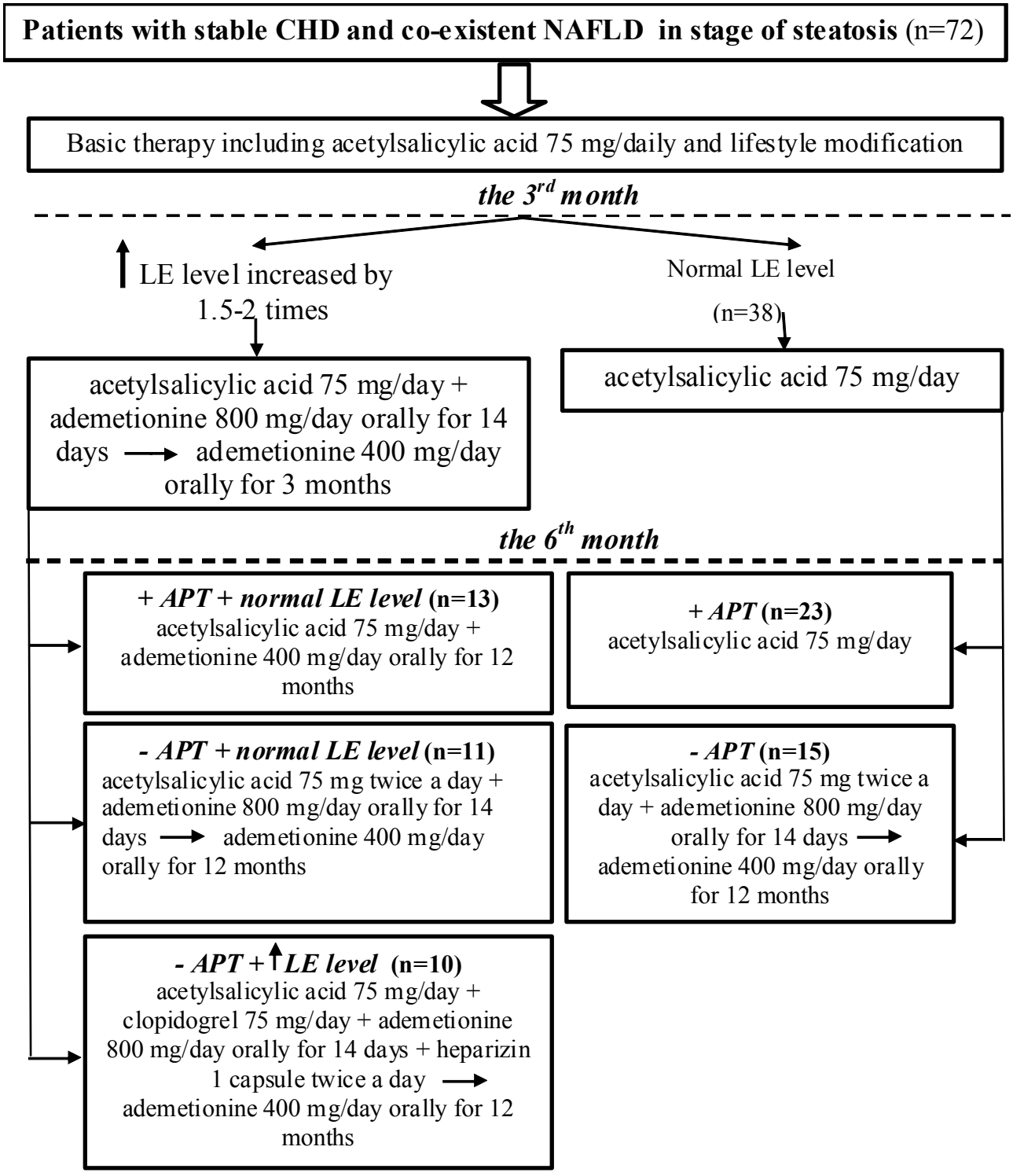


**Fig.1. Algorithm of antiplatelet and hepatoprotective differentiation therapy in patients with stable CHD and co-existent NAFLD in stage of steatosis depending on changes in the functional state of the liver on the background of treatment**

*Notes*: LE – liver enzymes (AST ALT, GGTP); - ¦ monitoring of liver function by serum levels of LE as compared to the basal level; «+» - sufficient control of platelet haemostasis; «-» - insufficient control of platelet haemostasis.

**Table 2. Dynamics of liver function indicators in patients with stable CHD and co-existent NAFLD in stage of steatosis, (M±m)**

| Indicator, units of measurement | Control group (n=20) | Patients with stable CHD and co-existent NAFLD in stage of steatosis (n=72) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Basal level | Group I (n=38) | | | Group II (n=34) | | | |
| | | | 3 months after treatment | 6 months after treatment | | 3 months after treatment | 6 months after treatment | | |
| | | | | subgroup A (n=23) | subgroup B (n=15) | | subgroup A (n=13) | subgroup B (n=11) | subgroup C (n=10) |
| AST, mmol/L | 0.38±0.06 | 0.42±0.03 | 0.41±0.03 | 0.39±0.01 | 0.43±0.02 | 0.74±0.07*§ | 0.40±0.02¶ | 0.43±0.04¶ | 0.49±0.05* §¶ |
| Δ | | | | -0.03 | +0.01 | | -0.02 | +0.01 | +0.07 |
| ALT, mmol/L | 0.27±0.05 | 0.30±0.04 | 0.28±0.02 | 0.27±0.04 | 0.29±0.03 | 0.54±0.06*§ | 0.28±0.03¶ | 0.33±0.02¶ | 0.42±0.04* §¶ |
| Δ | | | | -0.03 | -0.01 | | -0.02 | -0.03 | +0.12 |
| GGTP, mmol/L | 37.06±3.84 | 39.21±2.49 | 38.06±2.83 | 35.12±3.18 | 36.23±2.94 | 62.74±3.46*§ | 39.76±3.08¶ | 40.37±2.72¶ | 44.81±3.35*§¶ |
| Δ | | | | -4.09 | -2.98 | | +0.55 | +1.16 | +5.60 |

Notes: * – a reliable difference as compared to the control group ($p<0.05$); § – a reliable difference as compared to the basal level ($p<0.05$); ¶ – a reliable difference as compared to the indicator 3 months after treatment ($p<0.05$); Δ – difference between the indicator observed 6 months after treatment and the basal level

aggregation time increased by 23.8% and 19.2% as compared to the basal level ($p<0.05$); however, it did not reach the level of the control group. Aggregation rate decreased by 27.3% (Group IIA), 19.5% (Group IIB) and 18.8% (Group IIC) as compared to its basal level ($p<0.05$). In Group IIA, this indicator reached the level of the control group, while in Group IIB and Group IIC, it remained 11.9% and 12.8% higher than that in the control group ($p<0.05$). Moreover, the difference between the degree of aggregation 6 months after treatment and the basal level was more significant in patients of Group IIA constituting -8.87 as compared to -6.91 in patients of Group IIB and -6.36 in patients of Group IIC.

In patients of Group IIA, a six-month treatment resulted in the decrease in platelet count by 27.9% as compared to the initial values being 13.6% lower than this indicator 3 months after therapy ($p<0.05$). In Group IIB and Group IIC, these changes were less significant - their platelet count decreased by 22.5% and 19.1% as compared to the basal level ($p<0.05$); by 7.2% and 3.1% as compared to the indicator observed 3 months after treatment ($p>0.05$) that did not correspond to the level of the control group. Similar tendencies were observed when analyzing von Willebrand factor. In Group IIA, the difference between this indicator 6 months after treatment and the basal level was -67.18 as compared to -51.14 in Group IIB and -41.14 in Group IIC being 48.1%, 31.8% and 15.3% lower than this difference 3 months after treatment in Group IIA, Group IIB and Group IIC, respectively ($p<0.05$).

The assessment of the functional state of the liver 3 months after therapy revealed certain features of changes (Table 2). In 38 (52.8%) patients, the level of liver enzymes was within the control limits. However, in 34 (47.2%) patients, an increase in their level was observed, which necessitated the administration of appropriate hepatoprotective therapy (Fig.1). In patients of Group I, AST and ALT levels were within the normal range being 7.95 and 3.7% higher than those in the control group ($p>0.05$). GGTP level corresponded to that in the control group being 2.9% lower than its initial value ($p>0.05$). However, in patients of Group II, AST and ALT levels increased by 1.7 and 1.8 times as compared to their initial values ($p<0.05$). Moreover, GGTP level increased by 1.6 times as compared to its initial value ($p<0.05$).

Six months after treatment, the level of liver enzymes in Group I was stable corresponding to their level in the control group. In Group IA, AST level was 7.1% lower as compared to its initial value; in Group IB, it was 2.4% higher than its initial value ($p>0.05$). In patients of Group IA, a six-month treatment resulted in the decrease in ALT level by 10.0% as compared to its initial value; in patients of Group IB, a six-month treatment resulted in the decrease in ALT level by 3.3% as compared to its initial value ($p>0.05$). In patient of Group IA and Group IB, GGTP level decreased by 10.2% and 7.6%, respectively ($p>0.05$) as compared to its initial value.

In Group II, ambiguous changes in the functional state of the liver were observed 6 months after therapy. Liver enzymes reached the level of the control group in 24 (70.6%) patients. In 10 (29.4%) patients, there was observed a significant decrease in their level as compared to the indicator observed 3 months after treatment; the obtained indicator was significantly higher as compared to their basal level. Three months after treatment, AST level reached the level of the control group in patients of Group IIA and Group IIB, while in Group IIC, this indicator was 16.7% higher as compared to its initial value ($p<0.05$). ALT level was 40.0% higher as compared to its initial value ($p<0.05$) in patients of Group IIC. Moreover, in patients of Group IIA and Group IIB, the difference between GGTP level 6 months after treatment and the basal level was +0.55 and +1.16, while in patients of Group IIC, this indicator increased by 5.0, respectively.

Thus, the obtained results necessitated the development of differentiated approaches to long-term APT depending on the effectiveness of achieving sufficient control of platelet haemostasis. In particular, there was determined the possibility of using long-term monotherapy with acetylsalicylic acid, liver function monitoring, the inclusion of an appropriate scheme of hepatoprotective therapy and the correction of antiplatelet treatment 3 and 6 months after its administration if necessary in order to treat patients with stable CHD and co-existent NAFLD in stage of steatosis.

**Conclusions**

1. The use of long-term differentiation APT in patients

with stable CHD and co-existent NAFLD in stage of steatosis provides an effective monitoring of platelet haemostasis thereby reducing long-term cardiovascular risk.

2. To treat patients with stable CHD and co-existent NAFLD in stage of steatosis, it is reasonable to use a differentiated approach to APT, dynamic liver function monitoring and to include appropriate hepatoprotective drugs, if necessary.

3. The developed concept of differentiation treatment of patients with CHD and co-existent NAFLD in stage of steatosis envisages the need for monitoring the indicators of platelet haemostasis and liver function every three months after the administration of APT with the possibility of its intensification and the inclusion of hepatoprotective drugs according to the appropriate scheme depending on the increase in liver enzyme levels.

**Prospects for further research**

Further research should be directed at the development of new differentiated approaches to combination treatment of patients with CHD and co-existent NAFLD in stage of non-alcoholic steatohepatitis.

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